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Acting Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
US Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

June 16, 2000

Dear Susan:

I am writing to you at this time for several reasons: First to provide you with an update on how the development of the AFUD sponsored sexually-related personal distress scale is coming; second, to share some thoughts concerning the recently released FSD Draft Guidance document, and third to communicate my congratulations on your recent directorship.

Concerning the Female Sexual Distress Scale (FSDS), although we are still in the early stages of the research program, and awaiting the results of several clinical trials, I am very pleased with the results of the preliminary studies. Basically, I have summarized these findings in an enclosed packet of PowerPoint slides, the majority of which I presented at the AFUD Sexual Research Council meetings at the AUA in Atlanta recently. Together with the brief abstract I have included, I believe these tables and figures should give you a pretty good feel for how this program of research is going, and reinforce the viability of the idea of measuring and quantifying sexually-related personal distress.

As to the recently released FSD Draft Guidance, for the most part I believe it is very well conceived, clearly written, and deals effectively with the major nosologic and design issues in FSD clinical trials. The section on the role and importance of *Personal Distress* is clear and concise, and underlines the point that personal distress should be utilized as a design variable that insures a more homogeneous and relevant study sample, and additionally reduces within-groups heterogeneity, resulting in more power in the design.

Where I have difficulty with the Guidance is in the assignment of "...successful and satisfactory events or encounters" exclusivity as primary endpoints, and the concomitant relegation of psychometric operational definitions of constructs (e.g., sexual desire, sexual arousal) to secondary endpoint status .

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My concern is based on a number of considerations. To begin with, patient recording of events is no less "self-report" than the data derived from any self-report inventory, and thereby no more "objective" than any other self-report data. In addition, by its nature it is not easily amenable to the techniques of measurement science (e.g., reliability and validation studies), so the quality of such assessment is unknown and cannot be easily established.

Also, sexual behavior is often a poor proxy for underlying biological states (e.g., levels of sexual desire) because people engage in sexual activities for a variety of reasons (e.g., sense of duty, guilt, personal expectations, "keeping the peace"). The manifestation of these behaviors are mediated by numerous factors that are basically unrelated to the core biological events our treatments are designed to effect, thereby introducing unknown levels of error into our studies.

In addition, by "tallying" events or encounters we are essentially engaged in "counting", which is the most primitive and least sensitive form of measurement. Although it can be argued that if a treatment under investigation significantly effects such counts we can be fairly well assured that we are dealing with a true treatment difference, such a logic presumes a large and salient effect size. Because of the complex nature of female sexual functioning, I believe we are more likely to see ""moderate" effect sizes associated with our interventions, and will thereby run the risk of missing effective interventions because our primary endpoint measures are too coarse to detect them.

As an alternative approach, I would like to recommend that *both* events and encounters *and* well-validated psychometric outcomes measures (i.e., tests and rating scales) be considered as primary endpoints, both in tandem and independently. Specific determinations of which tests and rating scales are to be used would be established by convention, and be contingent upon the approval of the appropriate regulatory panel in any particular trial. In CNS trials, psychometric instruments have been utilized for decades as primary endpoints, not to the exclusion of behavioral data, but concomitant with it. I believe that such an approach would result in superior clinical trials that would not only possess the capacity to weed out ineffective treatments, but would also possess the sensitivity to maximally identify promising new agents and interventions.

I hope these observations have provided more light than smoke. I would be happy to discuss them with you further, and look forward to seeing you in Boston in October, where I hear we will be on the same panel.

Sincerely,

Leonard R. Derogatis, Ph.D.
Professor and Director
Co-Director, Organized Research Center for
Health Promotion and Disease Prevention

DEVELOPMENT OF THE FEMALE SEXUAL DISTRESS SCALE (FSDS): PRELIMINARY STUDIES

Leonard R. Derogatis, Ph.D.
University of Maryland, Baltimore

DRAFT

DRAFT

Abstract

Objectives: The primary objectives of the current research are to initiate the preliminary studies in a broad program of investigations designed to develop a new self-report instrument measuring sexually-related personal distress in women.

Background: Contemporary American and European nosological systems for the diagnosis of female sexual dysfunctions currently require manifest "personal distress" to be present (i.e., a necessary condition) to assign a diagnosis in six of eight major shared diagnostic categories. There are, however, no quantifiable standards available to document personal distress of this nature. Funded by the American Foundation for Urologic Disease, the current program of studies is designed to develop a brief, valid and reliable instrument to operationalize this important aspect of diagnostic assignment. and help establish nosologic homogeneity.

Methods: The preliminary studies reported here were conducted with the principal goals of, a.) establishing a rough prototype of the FSDS, b) transforming the rough prototype to a more polished prototype through item reduction, and c.) doing preliminary analyses of reliability and validity of the polished FSDS prototype. Samples involved included 60 non-dysfunctional, normal community women evaluated via mailed questionnaires, and a small sample of women (N=18) suffering from sexual dysfunctions, including hypoactive sexual desire disorder, arousal disorder, and orgasmic disorder were recruited from a variety of local sources. All were administered the 20-item rough prototype, in addition to inventories measuring affects balance, psychological symptoms, and personal history.

DRAFT

Results: Initial factor analysis identified 3 factors meeting eigenvalue and scree criteria that were rotated to an orthogonal varimax solution. Items which demonstrated substantial loadings on non-principal components or split loadings on multiple components were eliminated from the prototype. Remaining items were then subjected to a single unrotated principal components analysis (73% of the variance in the matrix) to insure they reflected univocal loadings on a single construct. Internal consistency and test-retest reliability coefficients were generated for each sample separately: coefficients α were .88 and .86 for patients and normals respectively, and test-retest coefficients were .91 for both groups. Using a cutoff score of 20, an evaluation of the discriminant validity of the 12-item prototype (i.e., its ability to distinguish patients from normals) was carried out. Sensitivity was observed to be 84%, specificity was 100%, and the predictive value of a positive was also 100 %. Errors in assignment were observed only with false negatives which revealed a rate of 16%.

Conclusions: Preliminary evaluations of the FSDS prototype show it to be a highly reliable and valid instrument that possesses substantial promise as a quantifiable indicator of sexually related personal distress.

Future Studies: The 12-item FSDS polished prototype has been included in three multicenter clinical drug trials, two evaluating interventions with Female Arousal Disorder, and a third investigating a treatment for Hypoactive Sexual Desire Disorder. These efforts are designed to further establish discriminant validity, and sensitivity to therapeutic intervention for the instrument.

(FSDS)
FEMALE SEXUAL DISTRESS SCALE
(Prototype I-A)

INSTRUCTIONS

Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and circle the number that best describes HOW OFTEN THAT PROBLEM HAS BOTHERED YOU OR CAUSED YOU DISTRESS DURING THE PAST _____30 DAYS_____ INCLUDING TODAY. Circle only one number for each item, and take care not to skip any items. If you change your mind, erase your first circle carefully. Read the example before beginning, and if you have any questions please ask about them.

Example: How often did you feel: **Personal responsibility for your sexual problems.**

NEVER	RARELY	OCCASIONALLY	FREQUENTLY	ALWAYS
0	1	2	3	4

HOW OFTEN DID YOU FEEL:

1.	Distressed about your sex life	0	1	2	3	4
2.	Anxious about your sexuality	0	1	2	3	4
3.	Unhappy about your sexual relationship	0	1	2	3	4
4.	Guilty about sexual difficulties	0	1	2	3	4
5.	That you are a poor sexual partner	0	1	2	3	4
6.	Frustrated by your sexual problems	0	1	2	3	4
7.	Stressed about sex	0	1	2	3	4
8.	No longer sexually attractive	0	1	2	3	4
9.	Inferior because of sexual problems	0	1	2	3	4
10.	Worried about sex	0	1	2	3	4
11.	Sexually inadequate	0	1	2	3	4
12.	Regrets about your sexuality	0	1	2	3	4
13.	Sexually unfulfilled	0	1	2	3	4
14.	Embarrassed about sexual problems	0	1	2	3	4
15.	Dissatisfied with your sex life	0	1	2	3	4
16.	Angry about your sex life	0	1	2	3	4
17.	Confused about sex	0	1	2	3	4
18.	Disappointed about sex	0	1	2	3	4
19.	Trapped in a poor sexual relationship	0	1	2	3	4
20.	Humiliated because of sex	0	1	2	3	4

(FSDS)
FEMALE SEXUAL DISTRESS SCALE
(Prototype II-A)

INSTRUCTIONS

Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and circle the number that best describes HOW OFTEN THAT PROBLEM HAS BOTHERED YOU OR CAUSED YOU DISTRESS DURING THE PAST _____30 DAYS_____ INCLUDING TODAY. Circle only one number for each item, and take care not to skip any items. If you change your mind, erase your first circle carefully. Read the example before beginning, and if you have any questions please ask about them.

Example: How often did you feel: **Personal responsibility for your sexual problems.**

NEVER	RARELY	OCCASIONALLY	FREQUENTLY	ALWAYS
0	1	2	3	4

HOW OFTEN DID YOU FEEL:

1.	Distressed about your sex life	0 1 2 3 4
3.	Unhappy about your sexual relationship	0 1 2 3 4
4.	Guilty about sexual difficulties	0 1 2 3 4
6.	Frustrated by your sexual problems	0 1 2 3 4
7.	Stressed about sex	0 1 2 3 4
9.	Inferior because of sexual problems	0 1 2 3 4
10.	Worried about sex	0 1 2 3 4
11.	Sexually inadequate	0 1 2 3 4
12.	Regrets about your sexuality	0 1 2 3 4
14.	Embarrassed about sexual problems	0 1 2 3 4
15.	Dissatisfied with your sex life	0 1 2 3 4
16.	Angry about your sex life	0 1 2 3 4

Principle Components Analysis

Structured Loading Analysis

Principle Component Loadings

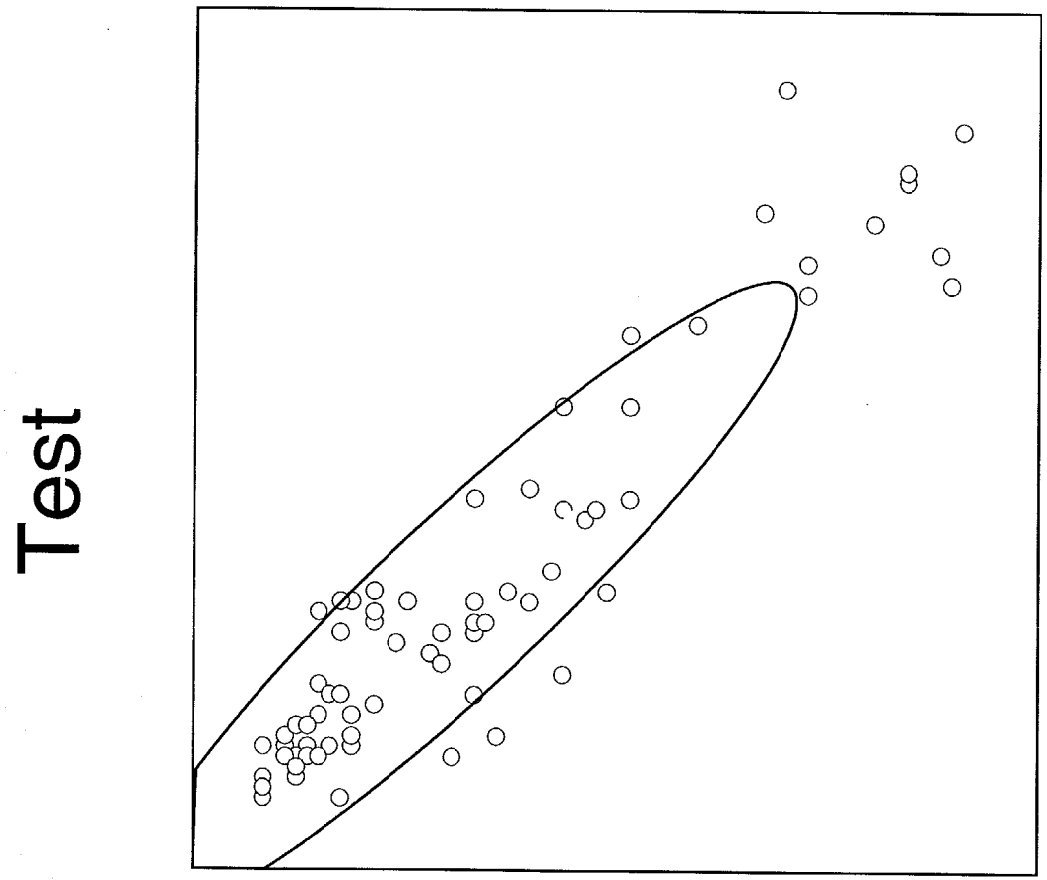
FSDS1	0.882
FSDS3	0.776
FSDS4	0.888
FSDS6	0.907
FSDS7	0.852
FSDS9	0.884
FSDS10	0.861
FSDS11	0.805
FSDS12	0.822
FSDS14	0.840
FSDS15	0.853
FSDS16	0.858

Percent of Total Variance Explained = **72.79**

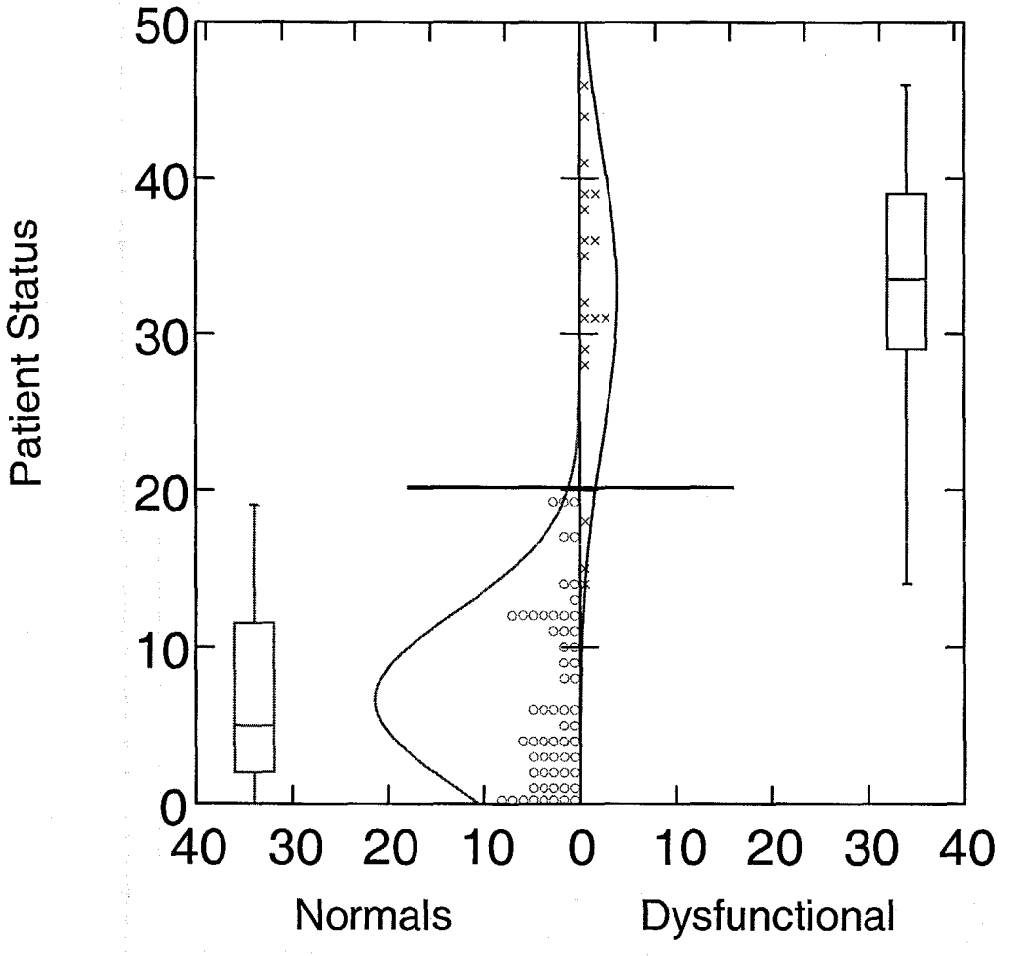
FSDS Reliability Coefficients
12 item FSDS

Sample	Coefficient α	R_{tt}
Sexual Dysfunction (N = 18)	0.88	0.91
Normals (N = 60)	0.86	0.91

FSDS - Test/Retest Scatterplot



Female Sexual Dysfunction Scale(FSDS)
12 Item Prototype (cut-off = 20)



Patient Status

○ Normals 60

× Sexual Dysfunction 18

FSDS - Functional vs. Dysfunctional Discrimination [cutoff = 20]

		Diagnosed	
		Dysfunction	Normal	
Predicted	Dysfunctional	15	0	15
	Normal	3	60	63
		18	60	78

Sensitivity	84%
Specificity	100%
False Positive	0%
False Negative	16%
Pos. Predic. Value	100%

Correlations between FSDS (12-Item) and Psychological Distress and Measures of Well-being

	FSDS 12-Item
BSI18-SOM	0.278
BSI18-DEP	**0.588**
BSI18-ANX	0.335
BSITOT	**0.526**
POSTOT	-0.560
NEGTOT	0.582
ABI	**-0.627**

FSDS - Pending Trials

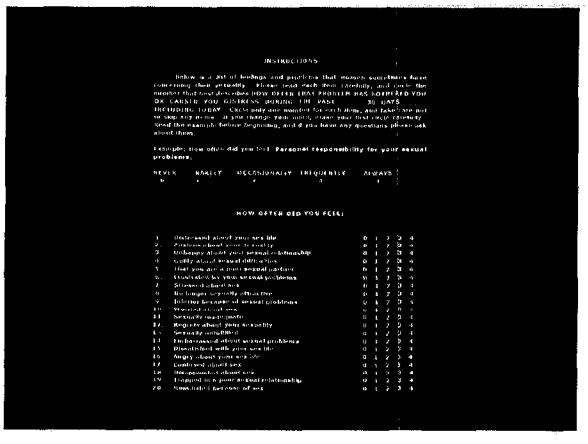
(1) Four arms - 3 Drug Doses & Placebo
Dx Female Arousal Disorder
N =40 per arm: 20 Frq./20 Intensity
Sensitivity to Treatment Intervention

(2) Four arms - 3 Drug Dose & Placebo
Dx: Female Arousal Disorder
N = 65 per arm: Frequency & Intensity - same form
Sensitivity to Treatment Intervention

(3) Two arms - No Drug Intervention
Dx: Hypoactive Sexual Desire Disorder
N = Not yet established
Discrimination of Functional versus Dysfunctional

Female Sexual Dysfunction Scale (FSDS) Preliminary Report

Leonard R. Derogatis, Ph.D.
University of Maryland, Baltimore



INSTRUCTIONS

Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and circle the number that best describes HOW OFTEN THAT PROBLEM HAS BOTHERED YOU OR CAUSED YOU DISTRESS DURING THE PAST 30 DAYS.

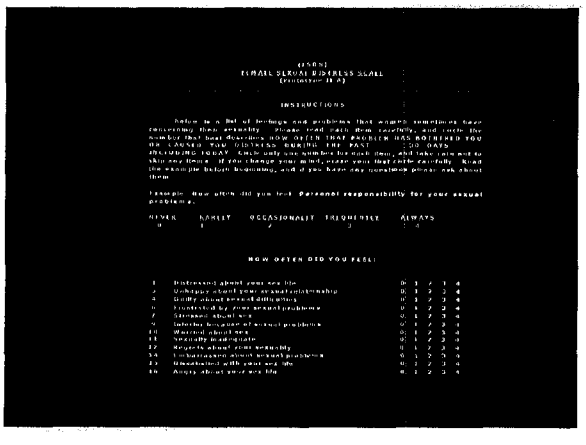
INTERCOURSE TODAY. Circle only one number for each item, and take care not to skip any items. If you change your mind, erase your first circle clearly. Read the example below beginning, and if you have any questions please ask about them.

Example: How often did you feel **Personal responsibility for your sexual problems.**

NEVER	RARELY	OCCASIONALLY	FREQUENTLY	ALWAYS
0	1	2	3	4

HOW OFTEN DID YOU FEEL:

1.	Distressed about your sex life	0	1	2	3	4
2.	Problems about trust in society	0	1	2	3	4
3.	Unhappy about your sexual relationship	0	1	2	3	4
4.	Guilty about sexual difficulties	0	1	2	3	4
5.	Hurt you as your sexual partner	0	1	2	3	4
6.	Frustrated by your sexual problems	0	1	2	3	4
7.	Stressed about sex	0	1	2	3	4
8.	No longer sexually attractive	0	1	2	3	4
9.	Inferior because of sexual problems	0	1	2	3	4
10.	Worried about sex	0	1	2	3	4
11.	Sexually inadequate	0	1	2	3	4
12.	Regret about your sexuality	0	1	2	3	4
13.	Sexually unaffected	0	1	2	3	4
14.	Embarrassed about sexual problems	0	1	2	3	4
15.	Disatisfied with your sex life	0	1	2	3	4
16.	Angry about your sex life	0	1	2	3	4
17.	Confused about sex	0	1	2	3	4
18.	Responsive about sex	0	1	2	3	4
19.	Trapped in a poor sexual relationship	0	1	2	3	4
20.	Uncomfortable with sex	0	1	2	3	4



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(Derogatis, 1997)

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Principle Components Analysis
Structured Loading Analysis

Principle Component Loadings

FSDS1	0.682
FSDS3	0.726
FSDS4	0.858
FSDS5	0.907
FSDS7	0.852
FSDS8	0.864
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FSDS12	0.822
FSDS14	0.826
FSDS15	0.955
FSDS16	0.955

Percent of Total Variance Explained = 72.79

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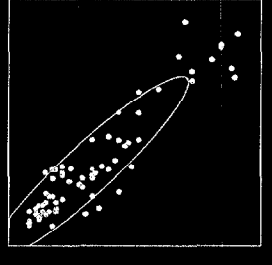
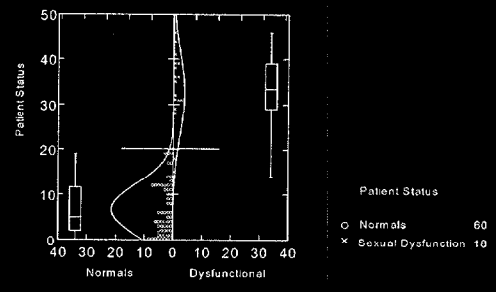


Female Sexual Dysfunction Scale(FSDS)



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Dx = Hypoactive Sexual Desire Disorder
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Discrimination of Functional versus Dysfunctional